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(54) Title: METHOD FOR THE PREPARATION OF 5-CYANO-1-(4-FLUOROPHENYL)-1,3-DIHYDROISOBENZOFURANS

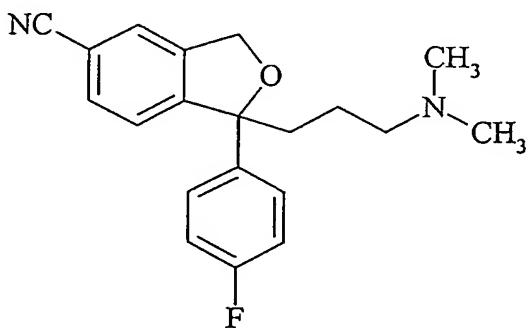
(57) Abstract: A method for the preparation of 5-cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran comprising conversion of a 5-substituted 1-(4-fluorophenyl)-1,3-dihydro-isobenzofuran derivative.

METHOD FOR THE PREPARATION OF 5-CYANO-1-(4-FLUOROPHENYL)-1,3-DIHYDROISOBENZOFURANS

The present invention relates to a method for the preparation of 5-cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran which is an intermediate used for the manufacture of the well-known antidepressant drug citalopram, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile.

Background of the Invention.

Citalopram is a well-known antidepressant drug that has now been on the market for some years and has the following structure:



Formula I

It is a selective, centrally active serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor, accordingly having antidepressant activities. The antidepressant activity of the compound has been reported in several publications, eg. J. Hyttel *Prog. Neuro-Psychopharmacol. & Biol. Psychiat.* 1982, 6, 277-295 and A. Gravem *Acta Psychiat. Scand.* 1987, 75, 478-486. The compound has further been disclosed to show effects in the treatment of dementia and cerebrovascular disorders, EP-A-474580.

Citalopram was first disclosed in DE 2,657,013, corresponding to US 4,136,193. This patent publication describes the preparation of citalopram by one method and outlines a further method, which may be used for preparing citalopram.

25

According to the process described, the corresponding 1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile is reacted with 3-(N,N-dimethylamino)propyl-

chloride in the presence of methylsulfinylmethide as condensing agent. The starting material was prepared from the corresponding 5-bromo derivative by reaction with cuprous cyanide.

5 International patent application No. WO 98/019511 discloses a process for the manufacture of citalopram wherein a (4-(cyano, alkyloxycarbonyl or alkylaminocarbonyl)-2-hydroxymethylphenyl-(4-fluorophenyl)methanol compound is subjected to ring closure. The resulting 5-(alkyloxycarbonyl or alkylaminocarbonyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran is converted to the corresponding 5-cyano derivative and the 5-cyano derivative is then alkylated with a (3-dimethylamino)propylhalogenide in order to obtain citalopram.

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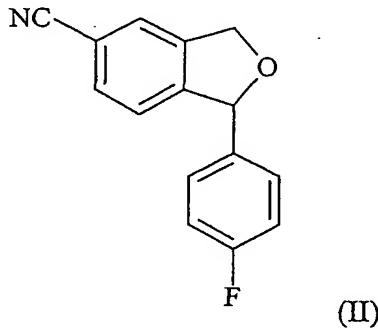
It has now, surprisingly, been found that citalopram may be manufactured by a novel favourable process where a 5-substituted 1-(4-fluorophenyl)-1,3-dihydroisobenzofuran is converted to the corresponding 5-cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran before being alkylated by a 3-dimethylaminopropyl-group.

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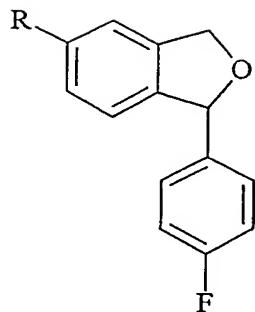
Description of the invention

Accordingly, the present invention relates to a novel method for the preparation of an intermediate in the preparation of citalopram having the formula

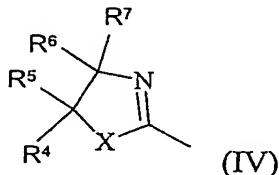
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by conversion of a compound of formula



wherein R is halogen, a group of the formula $\text{CF}_3\text{-(CF}_2\text{)}_n\text{-SO}_2\text{-O-}$, wherein n is 0-8, -
 OH, -CHO, - CH_2OH , - CH_2NH_2 , - CH_2NO_2 , - CH_2Cl , - CH_2Br , - CH_3 , - NHR^1 , -
 5 COOR^2 , - CONR^2R^3 wherein R^2 and R^3 are selected from hydrogen optionally substituted alkyl, aralkyl or aryl and R^1 is hydrogen or alkylcarbonyl, or a group of formula



wherein X is O or S;

10 R^4 - R^5 are each independently selected from hydrogen and C_{1-6} alkyl or R^4 and R^5 together form a C_{2-5} alkylene chain thereby forming a spiro ring; R^6 is selected from hydrogen and C_{1-6} alkyl, R^7 is selected from hydrogen, C_{1-6} alkyl, a carboxy group or a precursor group therefore, or R^6 and R^7 together form a C_{2-5} alkylene chain thereby forming a spiro ring.

15

This intermediate product of formula (II) may be converted to citalopram by alkylation as described above.

In another aspect, the present invention relates to an antidepressant pharmaceutical

20 composition comprising citalopram manufactured by the process of the invention.

According to one embodiment of the invention, wherein R is halogen, and the compound of formula (III) is converted to a compound of formula (II) by a reaction with a cyanide source optionally in the presence of a catalyst.

25

According to a further embodiment of the invention, wherein R is a triflate group of the formula $\text{CF}_3-(\text{CF}_2)_n-\text{SO}_2-\text{O}-$, wherein n is 0, 1, 2, 3, 4, 5, 6, 7 or 8, the compound of formula (III) is converted to a compound of formula (II) by reaction with a cyanide source optionally in the presence of a catalyst.

5

The cyano sources may conveniently be selected from a group consisting of cyanide sources such as NaCN , KCN , $\text{Zn}(\text{CN})_2$, $\text{Cu}(\text{CN})$ or $(\text{R''})_4\text{NCN}$ wherein each R'' represents $\text{C}_{1-8}\text{-alkyl}$ or optionally two R'' together with the nitrogen form a ring structure or combinations thereof.

10

The cyanide source is used in a stoichiometric amount or in excess, preferably 1-2 equivalents are used pr. equivalent starting material.

15

When R is halogen or a group of the formula $\text{CF}_3-(\text{CF}_2)_n-\text{SO}_2-\text{O}-$, wherein n is 0-8, the reaction of the present invention is performed in the presence or absence of a catalyst. The catalysts are *i.e.* $\text{Ni}(0)$, $\text{Pd}(0)$ or $\text{Pd}(\text{II})$ catalysts as described by Sakakibara et. al. in *Bull. Chem. Soc. Jpn.* 1988, 61, 1985-1990. Preferred catalysts are $\text{Ni}(\text{PPh}_3)_3$ or $\text{Pd}(\text{PPh}_3)_4$, or $\text{Ni}(\text{PPh})_2\text{Cl}$ or $\text{Pd}(\text{PPh})_2\text{Cl}_2$.

20

In a particularly preferred embodiment, a Nickel(0) complex is prepared *in situ* before the cyanide exchange reaction by reduction of a Nickel(II) precursor such as NiCl_2 or NiBr_2 by a metal, such as zinc, magnesium or mangan in the presence of excess of complex ligands, preferably triphenylphosphin.

25

The Pd or Ni-catalyst is conveniently used in an amount of 0.5-10, preferably 2-5 mol%.

In one embodiment of the invention, the reaction is carried out in the presence of a catalytic amount of Cu^+ or Zn^{2+} .

30

Catalytic amounts of Cu^+ and Zn^{2+} , respectively, means substoichiometric amounts such as 0.1 - 5, preferably 1 - 3 %. Conveniently, about $\frac{1}{2}$ eq. is used per eq. Pd.

Any convenient source of Cu⁺ and Zn²⁺ may be used. Cu⁺ is preferably used in the form of CuI and Zn²⁺ is conveniently used as the Zn(CN)₂ salt.

The reactions may be performed in any convenient solvent as described in Sakakibara et. al. in *Bull. Chem. Soc. Jpn.* 1988, 61, 1985-1990. Preferred solvents are acetonitril, ethylacetat, THF, DMF or NMP.

In one aspect of the invention, a compound of Formula IV wherein R is Cl is reacted with NaCN in the presence of a Ni(PPh₃)₃ which is preferably prepared *in situ* as described above.

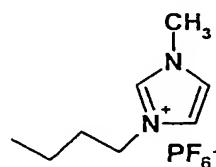
In another aspect of the invention, a compound of formula IV, wherein R is Br or I, is reacted with KCN, NaCN, CuCN or Zn(CN)₂ in the presence of Pd(PPh₃)₄. In a particular aspect of the invention, substoichiometric amounts of Cu(CN) and Zn(CN)₂ are added as recyclable cyanide sources.

In another aspect of the invention, a compound of formula IV, wherein R is Br or I, is converted to the corresponding cyano compound by reaction with Cu(CN) without catalyst. In a preferred embodiment, the reaction is performed at elevated temperature.

20

In a particular aspect of this invention, the cyanide exchange reaction is performed as a neat reaction *i.e.* without added solvent.

In another aspect of the invention, the cyanide exchange reaction is performed in an ionic liquid of the general formula (R')₄N⁺X⁻, wherein R' are alkyl-groups or two of the R' groups together form a ring and X⁻ is the counterion. In one embodiment of the invention, (R')₄N⁺X⁻ represents



30

In another particular aspect of this invention, the cyanide exchange reaction is conducted with apolar solvents such as benzene, xylene or mesitylene and under the influence of microwaves by using *i.e.* Synthewave 1000™ by Prolabo. In a particular aspect of this invention, the reaction is performed without added solvent.

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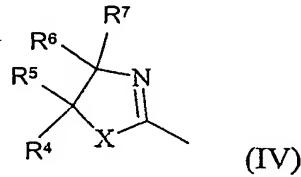
The temperature ranges are dependent upon the reaction type. If no catalyst is present, preferred temperatures are in the range of 100-200 °C. However, when the reaction is conducted under the influence of microwaves, the temperature in the reaction mixture may raise to above 300 °C. More preferred temperature ranges are between 120-170
10 °C. The most preferred range is 130-150 °C.

If catalyst is present, the preferred temperature range is between 0 and 100 °C. More preferred are temperature ranges of 40-90 °C. Most preferred temperature ranges are between 60-90 °C.

15

Other reaction conditions, solvents, etc. are conventional conditions for such reactions and may easily be determined by a person skilled in the art.

In another embodiment of the invention, wherein R is an oxazoline or a thiazoline
20 group of formula



wherein X, R⁴, R⁵, R⁶ and R⁷ are as defined above, the conversion to a cyano group may be carried out with a dehydration agent or alternatively, where X is S, by thermal
25 cleavage of the thiazoline ring or treatment with a radical initiator, such as peroxide or with light.

The dehydration agent may be any suitable dehydration agent conventionally used in the art, such as phosphoroxytrichloride, thionylchloride, phosphorpentachloride, PPA

(polyphosphoric acid) and P_4O_{10} . The reaction may be carried out in the presence of an organic base, such as pyridine or a catalytic amount of a tertiary amide.

Preferably, the oxazoline or thiazoline derivative of formula (IV) is treated with 5 $SOCl_2$ as a dehydrating agent and the reaction is carried out in toluene comprising a catalytic amount of N,N-dimethylformamide.

Alternatively, the dehydration agent may be a Vilsmeier reagent, i.e. a compound 10 which is formed by reaction of a chlorinating agent, preferably an acid chloride, e.g. phosgene, oxalyl chloride, thionyl chloride, phosphor oxychloride, phosphor pentachloride, trichloromethyl chloroformate, also briefly referred to as "diphosgene", or bis(trichloromethyl) carbonate, also briefly referred to as "triphosgene", with a tertiary amide such as N,N-dimethylformamide or a N,N-dialkylalkanamide, e.g N,N-dimethylacetamide. A classic Vilsmeier reagent is the 15 chloromethylenedimethyliminium chloride. The Vilsmeier reagent is preferably prepared *in situ* by adding the chlorinating agent to a mixture containing the starting oxazoline or thiazoline derivative of formula (IV) and the tertiary amide.

When X is S, the conversion of the thiazoline group of formula (IV) into the cyano 20 group is made by thermal transformation, the thermal decomposition of the thiazoline group is preferably carried out in an anhydrous organic solvent, more preferably an aprotic polar solvent, such as N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide or acetonitrile. The temperature at which the thermal decomposition transforms the 2-thiazolyl group to a cyano group is between 60 °C 25 and 140 °C. The thermal decomposition may conveniently be carried out by reflux in a suitable solvent, preferably acetonitrile. The thermal cleavage may conveniently be carried out in the presence of oxygen or an oxidation agent. A thiazoline group of formula (IV) where X is S and R⁷ is a carboxy group or a precursor for a carboxy group can also be converted to a cyano group by treatment with a radical initiator such 30 as light or peroxides.

According to a further embodiment of the invention, wherein R is a formaldehyde group, the compound of formula (III) is converted to a compound of formula (II) by

conversion of the aldehyde group to an oxime followed by dehydration of the oxime group.

The conversion of the formyl group to a cyano group may thus be carried out by 5 reaction with a reagent $R^8\text{-}V\text{-}NH_2$ wherein R^8 is hydrogen, lower alkyl, aryl or heteroaryl and V is O, N or S, followed by dehydration with a common dehydrating agent, for example thionylchloride, acetic anhydride/pyridine, pyridine/HCl or phosphor pentachloride. Preferred reagents $R^8\text{-}V\text{-}NH_2$ are hydroxylamin and compounds wherein R^8 is alkyl or aryl and V is N or O.

10

According to a further embodiment of the invention, wherein R is a -COOH group, the compound of formula (III) is converted to a compound of formula (II) by conversion to the amide via the corresponding acid chloride or an ester thereof followed by dehydration of the amide.

15

The acid chloride is conveniently obtained by treatment of the acid with $POCl_3$, PCl_5 or $SOCl_2$ neat or in a suitable solvent, such as toluene or toluene comprising a catalytic amount of N,N-dimethylformamide. The ester is obtained by treatment of the carboxylic acid with an alcohol, in the presence of an acid, preferably a mineral acid 20 or a Lewis acid, such as HCl , H_2SO_4 , $POCl_3$, PCl_5 or $SOCl_2$. Alternatively, the ester may be obtained from the acid chloride by reaction with an alcohol. The ester or the acid chloride is then converted to an amide by amidation with ammonia or a C₁₋₆ alkylamine, preferably t-butyl amine.

25 The conversion to amide may also be obtained by reaction of the ester with ammonia or an alkylamine under pressure and heating.

The amide group is then converted to a cyano group by dehydration. The dehydrating agent may be any suitable dehydrating agent, and the optimal agent may easily be 30 determined by a person skilled in the art. Examples of suitable dehydrating agents are $SOCl_2$, $POCl_3$ and PCl_5 , preferably $SOCl_2$.

In a particularly preferred embodiment, the carboxylic acid is reacted with an alcohol, preferably ethanol, in the presence of POCl_3 , in order to obtain the corresponding ester, which is then reacted with ammonia thereby giving the corresponding amide, which in turn is reacted with SOCl_2 in toluene comprising a catalytic amount of N,N-
5 dimethylformamide.

Alternatively, a compound where R is $-\text{COOH}$ may be reacted with chlorosulfonyl isocyanate in order to form the nitrile, or treated with a dehydrating agent and a sulfonamide as described in WO 00/44738.

10

Thus, a compound of formula (III) wherein R is a $-\text{COOR}^2$ group may be converted to a compound of formula (II) by conversion to the amide followed by dehydration.

15

Further, a compound of formula (III) wherein R is a $-\text{CONR}^2\text{R}^3$ group may be converted to a compound of formula (II) by dehydration to form the cyano group.

20

In another embodiment of the invention, wherein R is a $-\text{NHR}^1$ group, the compound of formula (III) is converted to a compound of formula (II) by hydrolysis to form a free amino group followed by diazotation of the free amino group and reaction with a cyanide source.

The cyanide source used is most preferably NaNO_2 , CuCN and/or NaCN . When R^1 is C_{1-6} alkylcarbonyl, it is initially subjected to hydrolysis thereby obtaining the corresponding compound wherein R^1 is H which is then converted as described above.

25

The hydrolysis may be performed either in acidic or basic environment.

Compounds of formula (III) wherein R is a $-\text{CH}_2\text{NO}_2$ group may be converted to a compound of formula (II) by treatment with TMSI to form the cyano group.

30

Compounds of formula (III) wherein R is a $-\text{CH}_2\text{NH}_2$ group may be converted to a compound of formula (II) by oxidation in presence of Copper(I)chloride to form the cyano group.

10

Compounds of formula (III) wherein R is a $-\text{CH}_2\text{Cl}$ group may be converted to a compound of formula (II) by reaction with AgNO_2 to form the corresponding $-\text{CH}_2\text{NO}_2$ group and followed by a treatment with TMSI to form the cyano group.

5 Compounds of formula (III) wherein R is a $-\text{CH}_2\text{Br}$ group, may be converted to a compound of formula (II) by reaction with AgNO_2 to form the corresponding $-\text{CH}_2\text{NO}_2$ group and followed by a treatment with TMSI to form the cyano group; or a treatment with NH_3 to form the corresponding $-\text{CH}_2\text{NH}_2$ group and followed by an oxidation in presence of Copper(I)chloride to form the cyano group.

10

Compounds of formula (III) wherein R is a $-\text{CH}_3$ group may be converted to a compound of formula (II) by treatment with a base and secondly with R^9ONO_2 , wherein R^9 is a C_{1-6} -alkyl, to form the corresponding $-\text{CH}_2\text{NO}_2$ group and followed by a treatment with TMSI to form the cyano group.

15

Compounds of formula (III) wherein R is a $-\text{CH}_2\text{OH}$ group may be converted to a compound of formula (II) by treatment with SOCl_2 or SOBr_2 to form the corresponding $-\text{CH}_2\text{Cl}$ group or $-\text{CH}_2\text{Br}$ group followed by conversion to cyano as described above.

20

Starting material of Formula (III) wherein R is halogen may be prepared as described in GB 1526331, compounds of Formula IV wherein R is $-\text{O}-\text{SO}_2-(\text{CF}_2)-\text{CF}_3$ and $-\text{OH}$ may be prepared analogous to the compounds described in WO 00/13648, compounds of Formula IV wherein R is an oxazoline or a thiazoline group may be prepared analogous to the compounds described in WO 00/23431, compounds of Formula IV wherein R is a $-\text{CH}_2\text{OH}$ group may be prepared analogous to the compounds described in PCT/DK/0100123, compounds of Formula IV wherein R is formaldehyde may be prepared analogously to the compounds described in WO 99/30548, compounds of Formula IV wherein R is $-\text{COOH}$, and esters and amides thereof may be prepared analogously to the compounds described in WO 98/19513 and compounds of Formula IV wherein R is $-\text{NHR}^1$ may be prepared analogously to the compounds described in WO 98/19512.

Citalopram is on the market as an antidepressant drug in the form of the racemate. However, in the near future the active S-enantiomer of citalopram is also going to be introduced to the market.

5 S-citalopram may be prepared by separation of the optically active isomers by chromatography.

Throughout the specification and claims, the term alkyl refers to a branched or unbranched alkyl group having from one to six carbon atoms inclusive, such as
10 methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl, 2,2-dimethyl-1-ethyl and 2-methyl-1-propyl.

Similarly, alkenyl and alkynyl, respectively, designate such groups having from two to six carbon atoms, including one double bond and triple bond respectively, such as
15 ethenyl, propenyl, butenyl, ethynyl, propynyl and butynyl.

The term aryl refers to a mono- or bicyclic carbocyclic aromatic group, such as phenyl and naphthyl, in particular phenyl.

20 The term aralkyl refers to aryl-alkyl, wherein aryl and alkyl is as defined above.

Halogen means chloro, bromo or iodo.

25 Citalopram may be used as the free base, in particular as the free base in crystalline form, or as a pharmaceutically acceptable acid addition salt thereof. As acid addition salts, such salts formed with organic or inorganic acids may be used. Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bismethylenesalicylic, methanesulfonic, ethanesulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic,
30 stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzene sulfonic and theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids.

The acid addition salts of the compounds may be prepared by methods known in the art. The base is reacted with either the calculated amount of acid in a water miscible solvent, such as acetone or ethanol, with subsequent isolation of the salt by 5 concentration and cooling, or with an excess of the acid in a water immiscible solvent, such as ethylether, ethylacetate or dichloromethane, with the salt separating spontaneously.

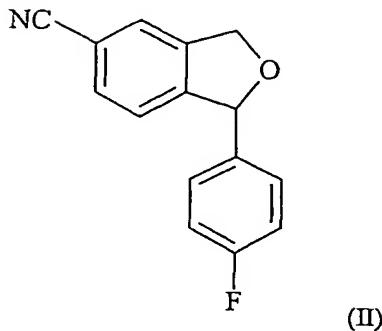
10 The pharmaceutical compositions of the invention may be administered in any suitable way and in any suitable form, for example orally in the form of tablets, capsules, powders or syrups, or parenterally in the form of usual sterile solutions for injection.

15 The pharmaceutical formulations of the invention may be prepared by conventional methods in the art. For example, tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a conventional tabletting machine. Examples of adjuvants or diluents comprise: Corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvant or additive, colourings, aroma, preservatives 20 etc. may be used provided that they are compatible with the active ingredients.

25 Solutions for injections may be prepared by solving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to the desired volume, sterilising the solution and filling it in suitable ampoules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

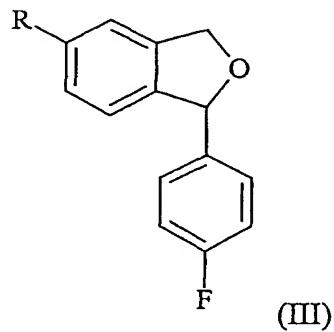
Claims

1. A method for the preparation of 5-cyano-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran

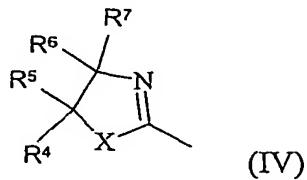


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comprising conversion of a 5-substituted 1-(4-fluorophenyl)-1,3-dihydroisobenzofuran derivative of the formula



wherein R represents halogen, a group of the formula $CF_3-(CF_2)_n-SO_2-O-$, wherein n is 0-8, -OH, -CHO, -CH₂OH, -CH₂NH₂, -CH₂NO₂, -CH₂Cl, -CH₂Br, -CH₃, -NHR¹, -COOR², -CONR²R³ wherein R² and R³ are selected from hydrogen optionally substituted alkyl, aralkyl or aryl and R¹ is hydrogen or alkylcarbonyl, or a group of formula



15

wherein X is O or S;

R⁴ – R⁵ are each independently selected from hydrogen and C₁₋₆ alkyl, or R⁴ and R⁵ together form a C₂₋₅ alkylene chain thereby forming a spiro ring; R⁶ is selected from hydrogen and C₁₋₆ alkyl, R⁷ is selected from hydrogen, C₁₋₆ alkyl, a carboxy group or

a precursor group therefore, or R⁶ and R⁷ together form a C₂₋₅ alkylene chain thereby forming a spiro ring.

2. The method of claim 1 wherein the intermediate product of formula (II) is converted to citalopram by alkylation; followed by isolation of citalopram or a pharmaceutical acceptable salt thereof.
3. The method of any of claims 1-2 wherein R is halogen, and the compound of formula (III) is converted to a compound of formula (II) by a reaction with a cyanide source optionally in presence of a catalyst.
4. The method of any of claims 1-2 wherein R is a triflate group of the formula CF₃-(CF₂)_n-SO₂-O-, wherein n is 0, 1, 2, 3, 4, 5, 6, 7 or 8, and the compound of formula (III) is converted to a compound of formula (II) by reaction with a cyanide source optionally in presence of a catalyst.
5. The method of any of claims 1-2 wherein R is an oxazoline or a thiazoline group of formula (IV), and the compound of formula (III) is converted to a compound of formula (II) by treatment with a dehydration agent, or alternatively where X is S, thermal cleavage of the thiazoline ring or treatment with a radical initiator, such as peroxide or with light.
6. The method of any of claims 1-2 wherein R is a formaldehyde group, and the compound of formula (III) is converted to a compound of formula (II) by conversion of the aldehyde group to an oxime followed by dehydration of the oxime group.
7. The method of any of claims 1-2 wherein R is a -COOH group, and the compound of formula (III) is converted to a compound of formula (II) by conversion to the amide via the corresponding acid chloride or an ester thereof followed by dehydration of the amide.

8. The method of any of claims 1-2 wherein R is a -COOR² group, and the compound of formula (III) is converted to a compound of formula (II) by conversion of the -COOR² group to an amide followed by dehydration.

5 9. The method of any of claims 1-2 wherein R is a -CONR²R³ group, and the compound of formula (III) is converted to a compound of formula (II) by dehydration of the -CONR²R³ group to form the cyano group.

10 10. The method of any of claims 1-2 wherein R is a -NHR¹ group, and the compound of formula (III) is converted to a compound of formula (II) by hydrolysis to form a free amino group followed by diazotation of the free amino group and reaction with a cyanide source.

15 11. The method of any of claims 1-2 wherein R is a -CH₂NO₂ group, and the compound of formula (III) is converted to a compound of formula (II) by treatment with TMSI to form the cyano group.

20 12. The method of any of claims 1-2 wherein R is a -CH₂NH₂ group, and the compound of formula (III) is converted to a compound of formula (II) by oxidation in presence of Copper(I)chloride to form the cyano group.

25 13. The method of any of claims 1-2 wherein R is a -CH₂Cl group, and the compound of formula (III) is converted to a compound of formula (II) by reaction with AgNO₂ to form the corresponding -CH₂NO₂ group and followed by a treatment with TMSI to form the cyano group.

14. The method of any of claims 1-2 wherein R is a -CH₂Br group, and the compound of formula (III) is converted to a compound of formula (II) by reaction with AgNO₂ to form the corresponding -CH₂NO₂ group and followed by a treatment 30 with TMSI to form the cyano group;
or a treatment with NH₃ to form the corresponding -CH₂NH₂ group and followed by an oxidation in the presence of Copper(I)chloride to form the cyano group.

15. The method of any of claims 1-2 wherein R is a -CH₃ group, and the compound of formula (III) is converted to a compound of formula (II) by treatment with a base and secondly with R⁹ONO₂, wherein R⁹ is a C₁₋₆-alkyl, to form the corresponding -CH₂NO₂ group and followed by a treatment with TMSI to form the cyano group.

16. The method of any of claims 1-2 wherein R is a -CH₂OH group, and the compound of formula (III) is converted to a compound of formula (II) by treatment with SOCl₂ or SOBr₂ to form the corresponding -CH₂Cl group or -CH₂Br group followed by

i) by reaction with AgNO₂ to form the corresponding -CH₂NO₂ group and followed by a treatment with TMSI to form the cyano group; or

15 ii) treatment with NH₃ to form the corresponding -CH₂NH₂ group and followed by an oxidation in presence of Copper(I)chloride to form the cyano group.

17. The method of any of claims 3-4 and 10 wherein the cyanide source is selected from KCN, NaCN, Zn(CN)₂, CuCN (R'')₄N(CN) wherein each R'' represents C₁₋₈-alkyl optionally two R'' together with the nitrogen form a ring structure, or combinations thereof.

18. The method of any of claims 3-4 and 10 wherein Zn²⁺ or Cu⁺ is added in substoichiometric amounts in combination with another cyanide source.

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19. An antidepressant pharmaceutical composition comprising citalopram manufactured by the method of any of claims 1 to 18.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 01/00186

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 307/87

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE, DK, FI, NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	US 4136193 A (KLAUS P. BOGESO ET AL), 23 January 1979 (23.01.79) --	1-19
X	Eur. J. Med. Chem. - Chimica Therapeutica, Volume 12, No 3, 1977, Allan J. Bigler et al, "Quantitative structure-activity relationships in a series of selective 5-HT uptake inhibitors" page 289 - page 295 --	1-19
X	WO 9819511 A2 (H. LUNDBECK A/S), 14 May 1998 (14.05.98) --	1-19

 Further documents are listed in the continuation of Box C. See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent but published on or after the international filing date
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INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 01/00186

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Information on patent family members

28/05/01

International application No.

PCT/DK 01/00186

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